

Mechanisms of vascular dysfunction in mice with endothelium-specific deletion of the PPAR-delta gene.

Journal: Am J Physiol Heart Circ Physiol

Publication Year: 2014

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PubMed link: 24486511

Funding Grants: Metabolically-driven epigenetic changes in iPSC reprogramming

Public Summary:

Peroxisome proliferator-activated receptor (PPAR)- is a nuclear hormone receptor that is mainly involved in lipid metabolism. Recent studies have suggested that PPAR- agonists exert vascular protective effects. The present study was designed to characterize vascular function in mice with genetic inactivation of PPAR- in the endothelium. Mice with vascular endothelial cell-specific deletion of the PPAR- gene (ePPAR/ mice) were generated using loxP/Cre technology. ePPAR/ mice were normotensive and did not display any sign of metabolic syndrome. Endothelium-dependent relaxations to ACh and endothelium-independent relaxations to the nitric oxide (NO) donor diethylammonium (Z)-1-(N,N-diethylamino)diazen-1-ium-1,2-diolate were both significantly impaired in the aorta and carotid arteries of ePPAR/ mice (P 0.05). In ePPAR/ mouse aortas, phosphorylation of endothelial NO synthase at Ser1177 was significantly decreased (P 0.05). However, basal levels of cGMP were unexpectedly increased (P 0.05). Enzymatic activity of GTP-cyclohydrolase I and tetrahydrobiopterin levels were also enhanced in ePPAR/ mice (P 0.05). Most notably, endothelium-specific deletion of the PPAR- gene significantly decreased protein expressions of catalase and glutathione peroxidase 1 and resulted in increased levels of H₂O₂ in the aorta (P 0.05). In contrast, superoxide anion production was unaltered. Moreover, treatment with catalase prevented the endothelial dysfunction and elevation of cGMP detected in aortas of ePPAR/ mice. The findings suggest that increased levels of cGMP caused by H₂O₂ impair vasodilator reactivity to endogenous and exogenous NO. We speculate that chronic elevation of H₂O₂ predisposes PPAR-- deficient arteries to oxidative stress and vascular dysfunction.

Scientific Abstract:

Peroxisome proliferator-activated receptor (PPAR)-delta is a nuclear hormone receptor that is mainly involved in lipid metabolism. Recent studies have suggested that PPAR-delta agonists exert vascular protective effects. The present study was designed to characterize vascular function in mice with genetic inactivation of PPAR-delta in the endothelium. Mice with vascular endothelial cell-specific deletion of the PPAR-delta gene (ePPARdelta(-/-) mice) were generated using loxP/Cre technology. ePPARdelta(-/-) mice were normotensive and did not display any sign of metabolic syndrome. Endothelium-dependent relaxations to ACh and endothelium-independent relaxations to the nitric oxide (NO) donor diethylammonium (Z)-1-(N,N-diethylamino)diazen-1-ium-1,2-diolate were both significantly impaired in the aorta and carotid arteries of ePPARdelta(-/-) mice (P < 0.05). In ePPARdelta(-/-) mouse aortas, phosphorylation of endothelial NO synthase at Ser(1177) was significantly decreased (P < 0.05). However, basal levels of cGMP were unexpectedly increased (P < 0.05). Enzymatic activity of GTP-cyclohydrolase I and tetrahydrobiopterin levels were also enhanced in ePPARdelta(-/-) mice (P < 0.05). Most notably, endothelium-specific deletion of the PPAR-delta gene significantly decreased protein expressions of catalase and glutathione peroxidase 1 and resulted in increased levels of H₂O₂ in the aorta (P < 0.05). In contrast, superoxide anion production was unaltered. Moreover, treatment with catalase prevented the endothelial dysfunction and elevation of cGMP detected in aortas of ePPARdelta(-/-) mice. The findings suggest that increased levels of cGMP caused by H₂O₂ impair vasodilator reactivity to endogenous and exogenous NO. We speculate that chronic elevation of H₂O₂ predisposes PPAR-delta-deficient arteries to oxidative stress and vascular dysfunction.